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CaO-catalyzed Aerobic Oxidation of α-Hydroxy Ketones: Application to One-pot Synthesis of Quinoxaline Derivatives

Takayoshi Hara, Yukihiro Takami, Nobuyuki Ichikuni, and Shogo Shimazu*
Graduate School of Engineering, Chiba University, 1-33 Yayoi, Inage-ku, Chiba 263-8522

(Received January 31, 2012; CL-120081; E-mail: shimazu@faculty.chiba-u.jp)

The aerobic oxidation of α-hydroxy ketones into α-diketones catalyzed by CaO is compared with the same reaction catalyzed by other metal oxides. The catalytic activities of the various metal oxides were proportional to their surface basicities. The direct conversion of α-hydroxy ketones into quinoxalines via CaO-catalyzed aerobic oxidation followed by in situ reaction with 1,2-diaminoaromatics is also achieved. Various types of quinoxalines were synthesized in the presence of the CaO catalyst and molecular oxygen. It was also found that the CaO catalyst was reusable without any loss of its catalytic activity.

Currently, the development of sustainable protocols using abundant and inexpensive catalysts is becoming progressively more important. From this viewpoint, alkaline earth metals are some of the most promising elements for use as catalysts. Among the alkaline earth metals, calcium seems to be an ideal candidate because it is essentially nontoxic, cheap, and abundant in the earth's crust.[1] From the point of "the Element Strategy,"[2] proposed by the Japanese government, the use of ubiquitous elements such as calcium instead of rare elements as catalytically active species in organic transformations is strongly desired.

Calcium oxide (CaO) is well known as a versatile heterogeneous catalyst. Regarding the application of CaO, a wide variety of base-catalyzed reactions, such as transesterification,[3a,3b] several carbon–carbon bond-forming reactions,[3c–3f] the isomerization or hydrogenation of dienes,[3g–3i] the dehydrogenation of ethylbenzene combined with CO_2 shift reaction,[3j] and urea synthesis,[3k] have been developed. However, there are no reports of aerobic alcohol oxidation into the corresponding carbonyl compounds by CaO catalyst. Herein, we describe the use of CaO in oxidative dehydrogenation of α-hydroxy ketones into α-diketones in the presence of molecular oxygen.

α-Diketones are useful building-block chemicals for the synthesis of various pharmaceuticals and porphyrin rings.[4] Although various oxidizing reagents, for example, acetic anhydride/DMSO,[5a] $(NH_4)_2Ce(NO_3)_6$,[5b] $Tl(NO_3)_3$,[5c] $SbCl_5$/DMSO,[5d] $Zn(BiO_3)_2$,[5e] CsOH,[5f] and NaH[5g] are generally available to perform this direct dehydrogenation, these reagents are often harmful and toxic, and considerable amounts are required. The oxidation of α-hydroxy ketones with molecular oxygen, performed with various transition-metal catalysts such as Pd,[6a] Ru,[6b] Zn,[6c] Co,[6d] V,[6e,6f] and Mo[6g,6h] has also been reported. Because of environmental concerns, there is a strong demand for a clean catalytic methodology for the conversion of α-hydroxy ketones to α-diketones.

Calcium oxide (99.9%) used in this study was purchased from Wako Pure Chemicals Ind. Co., Ltd., and its surface area estimated by BET method was 11 $m^2 g^{-1}$.[7] To begin our study, we assessed the ability of various metal oxides to serve as catalysts for the oxidation of benzoin (**1a**) without solvent under an atmospheric pressure of O_2 at 130 °C (Figure 1). Tanaka and Ozaki reported on the acid–base properties of metal oxides according to the electronegativity of metal ion (χ_i), which is obtained by the following equation: $\chi_i = (1 + 2Z)\chi_0$, where Z and χ_0 are the charge of metal ion and the electronegativity of neutral atom ($Z = 0$) given by Pauling, respectively.[9] As a result of the relationship between χ_i of each metal oxide catalyst and its catalytic activity, the reaction rate was inversely proportional to the catalyst's χ_i value, indicating the surface basic function plays a key role in the successful catalytic oxidation of **1a**.

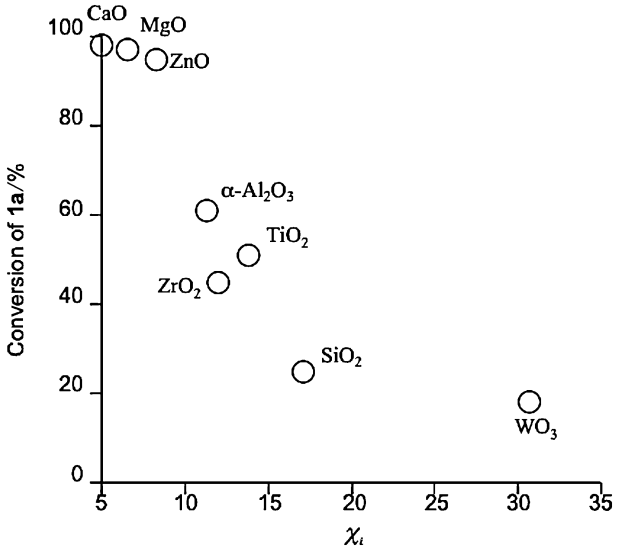
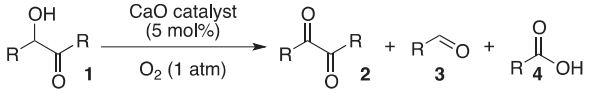


Figure 1. The relationship between the electronegativity of metal cations and conversion of **1a**. Reaction conditions: **1a** (1.5 mmol), catalyst (0.05 mmol), O_2 (1 atm), 130 °C, 1 h.

With the optimized reaction conditions in hand, different α-hydroxy ketones were investigated (Table 1).[10] CaO acted as an effective catalyst for this oxidation, and 63% benzil (**2a**), 5% benzaldehyde (**3a**), and 10% benzoic acid (**4a**) were obtained, respectively (Entry 1).[11] Under air flow (5 mL min^{-1}), the reaction rate decreased substantially (Entry 2). A small amount of **2a** was formed under a N_2 atmosphere without formation of **3a** and **4a**, presumably due to the acceptor-free dehydrogenation (Entry 3). Under 1 atm of CO_2, the dehydrogenation reaction did not proceed in the presence of CaO catalyst (Entry 4). Almost no reaction was observed in the absence of CaO (Entry 11). After the **1a** oxidation, the spent CaO catalyst was easily separated by simple centrifugation or filtration after the addition of toluene. In the XRD profile of the recovered CaO catalyst, the broad and weak peaks assignable to $Ca(OH)_2$ phase were observed.[12] After calcination under air at 700 °C for 1 h, high crystalline CaO was

Table 1. Aerobic oxidation of various α-hydroxy ketones using CaO catalyst[a]



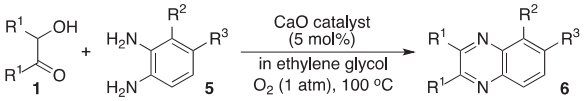
1a: R = Ph
1b: R = (4-CH_3)Ph
1c: R = (4-OCH_3)Ph
1d: R = 2-pyridyl
1e: R = 2-furyl
1f: R = ethyl

2a, 3a, 4a: R = Ph
2b, 3b, 4b: R = (4-CH_3)Ph
2c, 3c, 4c: R = (4-OCH_3)Ph
2d, 3d, 4d: R = 2-pyridyl
2e, 3e, 4e: R = 2-furyl
2f, 3f, 4f: R = ethyl

Entry	Substrate	Temp /°C	Time /h	Convn. /%[b]	Yield/%[b]		
					2	**3**	**4**
1	**1a**	130	1	96	63	5	10
2[c]	**1a**	130	1	48	38	3	6
3[d]	**1a**	130	1	14	12	n.d.[k]	n.d.
4[e]	**1a**	130	1	2	2	n.d.	n.d.
5[f]	**1a**	130	1	93	60	3	3
6[g]	**1b**	90	24	80	71	n.d.	3
7[g]	**1c**	100	12	89	76	n.d.	4
8	**1d**	100	1	96	95	n.d.	n.d.
9[g]	**1e**	100	6	90[h]	60	n.d.	1
10	**1f**	130	3	22[i]	20[i]	n.d.[i]	n.d.[i]
11[j]	**1a**	130	1	5	2	n.d.	n.d.

[a]CaO catalyst (5 mol %), **1** (1 mmol), and O_2 (1 atm). [b]Determined by HPLC using an internal standard. [c]Under air flow (5 mL min^{-1}). [d]Under N_2. [e]Under 1 atm of CO_2. [f]Reuse experiment. [g]Ethylene glycol (3 mL) was used as a solvent. [h]Formation of brown caramel was observed. [i]Determined by GC analysis. [j]Without catalyst. [k]n.d.: not detected.

Table 2. One-pot synthesis of quinoxalines **6** using CaO catalyst[a]



5a: $R^2 = R^3 = H$
5b: $R^2 = H$, $R^3 = CH_3$
5c: $R^2 = CH_3$, $R^3 = H$
5d: $R^2 = H$, $R^3 = OCH_3$
5e: $R^2 = H$, $R^3 = Cl$

6aa: $R^1 = Ph$, $R^2 = R^3 = H$
6ba: $R^1 = (4\text{-}CH_3)Ph$, $R^2 = R^3 = H$
6ca: $R^1 = (4\text{-}OCH_3)Ph$, $R^2 = R^3 = H$
6da: R^1 = 2-pyridyl, $R^2 = R^3 = H$
6ea: R^1 = 2-furyl, $R^2 = R^3 = H$
6fa: R^1 = ethyl, $R^2 = R^3 = H$
6ab: $R^1 = Ph$, $R^2 = H$, $R^3 = CH_3$
6ac: $R^1 = Ph$, $R^2 = CH_3$, $R^3 = H$
6ad: $R^1 = Ph$, $R^2 = H$, $R^3 = OCH_3$
6ae: $R^1 = Ph$, $R^2 = H$, $R^3 = Cl$

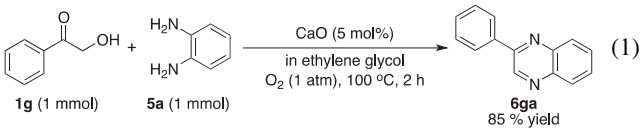
Entry	α-Hydroxyketone	Diamine	Temp /°C	Time /h	Product	Yield of **6** /%[b]
1	**1a**	**5a**	130	1	**6aa**	93
2[c]	**1b**	**5a**	100	3	**6ba**	97
3	**1c**	**5a**	100	3	**6ca**	94
4	**1d**	**5a**	80	8	**6da**	94
5[c]	**1e**	**5a**	100	3	**6ea**	69
6	**1f**	**5a**	100	24	**6fa**	27[d]
7	**1a**	**5b**	130	2	**6ab**	88
8	**1a**	**5c**	130	3	**6ac**	86
9	**1a**	**5d**	130	3	**6ad**	87
10	**1a**	**5e**	130	2	**6ae**	92

[a]CaO catalyst (5 mol %), **1** (1 mmol), **5** (1.5 mmol), ethylene glycol (3 mL), and O_2 (1 atm). [b]Determined by HPLC using an internal standard technique. [c]**5** (1 mmol). [d]48% of 2-ethylbenzimidazole (**7fa**) was formed.

reconstructed and could be reused without any loss of its high activity and selectivity (Entry 5).[13] Substituted benzoin derivatives such as *p*-toluoin (**1b**) or *p*-anisoin (**1c**) were also oxidized into the corresponding α-diketones with some degree of formation of the cleavage product (Entries 6 and 7). Among the reactions of α-hydroxy ketones, including heterocycles, the selective dehydrogenation of α-pyridoin (**1d**) occurred, and an almost quantitative yield of α-pyridil (**2d**) was obtained within 1 h (Entry 8). When α-furoin (**1e**) was used as a substrate, the production of a brown caramel-like substance was observed accompanied by the formation of α-furil (**2e**) (Entry 9). An aliphatic α-hydroxy ketone, propioin (**1f**), was transformed into 3,4-hexanedione (**2f**) using the current catalytic system (Entry 10). Although the present catalytic system was effective for the oxidation of α-hydroxy ketones, several limitations regarding substrates were observed. For example, the CaO-catalyzed oxidation of the α-hydroxy alcohol, dihydrobenzoin, did not proceed at all. Furthermore, the oxidations of methyl mandelate classified with α-hydroxy ester, and secondary alcohols such as benzhydrol and 2-adamantanol with the CaO catalyst were relatively slow. In the case of the oxidation of **1a** in the presence of **2a**, it should be noted that the selectivity for **3a** and **4a** increased with increasing amounts of the **2a**; thus the oxidative cleavage reaction might be enhanced by α-diketones formed in situ.[14]

To achieve the selective transformation of α-hydroxy ketones, this CaO catalyst system was applied to the one-pot synthesis of quinoxaline derivatives using α-hydroxy ketones and *o*-phenylenediamines.[15] Quinoxaline derivatives are well known because of their functions as the heterocyclic core of anticancer,[16a] antibacterial,[16b] and many pharmaceutical reagents,[16c–16e] due to the biological activities of these compounds. There are many methods of preparing quinoxalines, however, condensation between an α-diketone and a 1,2-diaminoaromatic is regularly employed.[17]

In view of the success of this CaO-catalyzed one-pot synthesis of quinoxalines, the scope and limitations of this reaction were explored (Table 2).[18] First, substrate compatibility was investigated by varying the α-hydroxy ketone used as the starting material. Both aromatic and heterocyclic substrates react successfully in the current one-pot reaction system (Entries 1–4). When using **1e** as the substrate, the formation of a caramel-like substance could not be inhibited (Entry 5). Aliphatic α-hydroxy ketone such as **1f** were found to be less selective because of the formation of 2-ethylbenzimidazole (**7fa**) with carboxylic acid as a cleavage product (Entry 6). In the case of substituted 1,2-diaminoaromatics, the one-pot reaction efficiently proceeded to produce the corresponding quinoxalines with high yields (Entries 7–10). Moreover, the one-pot quinoxaline synthesis using α-hydroxy acetophenone, an asymmetric α-hydroxy ketone, proceeded efficiently in the presence of the CaO catalyst, as highlighted in eq 1. The facile trapping of α-diketone formed in situ by a cascade cyclization with a 1,2-diaminoaromatic is a key step in achieving the selective synthesis of quinoxaline derivatives.[19]



(1)

In conclusion, the CaO-catalyzed aerobic oxidation of α-hydroxy ketones and its application in one-pot quinoxaline synthesis were demonstrated. The CaO catalyst could be reused without any loss of its high catalytic activity and selectivity. Further mechanistic studies and the development of other CaO-catalyzed organic transformations are now in progress.

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7 The BET surface area of the recovered CaO catalyst calcined at 700 °C for 1 h was 18 $m^2 g^{-1}$, and the CO_2-TPD profiles of fresh and recovered CaO catalysts were shown in Supporting Information.[8]
8 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
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10 Typical procedure of CaO-catalyzed aerobic oxidation of **1a**: Into a Schlenk tube with a reflux condenser was placed **1a** (1 mmol, 0.212 g) and CaO catalyst (0.05 mmol, 0.0028 g). The resulting mixture was stirred at 130 °C for 1 h under atmospheric pressure of O_2. **1a** conversion and **2a** yield were periodically determined by HPLC analysis using biphenyl as an internal standard.
11 In 1982, P. M. Keehn, et al. reported that a stoichiometric amount of $Ca(OCl)_2$ promoted the oxidative cleavage of α-hydroxy ketones into aldehydes and carboxylic acids, see: S. O. Nwaukwa, P. M. Keehn, *Tetrahedron Lett.* **1982**, *23*, 3135. In our catalysis, the oxidation of **3a** with the CaO catalyst also proceeded smoothly and 44% of **4a** was formed after 1 h under the same conditions.
12 The aerobic oxidation of **1a** in the presence of a $Ca(OH)_2$ catalyst instead of CaO also proceeded under the same reaction conditions. For the results of the catalytic reaction and the XRD profiles of recovered catalyst, see SI.[8]
13 After the oxidation of **1a**, adsorbed **2a** was detected by FT-IR analysis. The strong adsorption of the α-diketone onto the surface of CaO may be the cause of the lack of mass balance. Furthermore, the recovered CaO catalyst without calcination was able to promote this aerobic oxidation of **1a**, see SI.[8]
14 The data are shown in SI. Furthermore, the addition of catalytic amounts of radical scavengers (1 equivalent relative to Ca), such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO), hydroquinone, galvinoxyl, or 2,6-di-*tert*-butyl-*p*-cresol, did not affect the oxidation rate or product selectivity.
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18 Typical procedure of CaO-catalyzed one-pot synthesis of **6aa**: Into a Schlenk tube with a reflux condenser was placed **1a** (1 mmol, 0.212 g), **5a** (1.5 mmol, 0.162 g), and CaO catalyst (0.05 mmol, 0.0028 g). The resulting mixture was stirred at 130 °C for 1 h under atmospheric pressure of O_2. **1a** conversion and **6aa** yield were periodically determined by HPLC analysis using biphenyl as an internal standard.
19 During this one-pot reaction, α-diketone intermediate was not detected by HPLC analysis, see SI.[8]

